
MINISTRY OF AGRICULTURE, FISHERIES AND FOOD

# FOOD ADDITIVES AND CONTAMINANTS COMMITTEE REPORT ON CYCLAMATES

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**Food Additives and Contaminants Committee**

The terms of reference of the Food Additives and Contaminants Committee are:

To advise the Minister of Agriculture, Fisheries and Food, the Secretary of State for Scotland, the Minister of Health, and as respects Northern Ireland, the Secretary of State for the Home Department, on matters referred to them by Ministers, in relation to food contaminants, additives and similar substances which are or may be present in food, or used in its preparation, with particular reference to the exercise of powers conferred on Ministers by Sections 4, 5 and 7 of the Food and Drugs Act, 1955 and the corresponding provisions in enactments relating to Scotland and Northern Ireland.

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**Pharmacology Sub-Committee**

The terms of reference of the Pharmacology Sub-Committee are:

To advise, at the request of the Food Additives and Contaminants Committee or the Committee on Medical and Nutritional Aspects of Food Policy, on the hazard to health of the consumer, including toxicological and carcinogenic risk, arising from the presence of additives and contaminants in foods.

The members of the Pharmacology Sub-Committee are:

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# FOOD ADDITIVES AND CONTAMINANTS COMMITTEE

## Report on Cyclamates

### Terms of Reference

1. We were asked to review the proposal to allow the use of cyclamates in food in the light of certain additional evidence and to make recommendations.

### Report of Pharmacology Sub-Committee

2. We have received the report from our Pharmacology sub-Committee which is contained in Appendix I. We accept their conclusions and note particularly their remarks on the impressive extent of the information available to support the safety-in-use of cyclamates.

### Recommendations

3. We consider that since cyclamates do not appear to produce any toxic effects, since the amounts likely to be ingested will not be of an order likely to produce a significant laxative effect and since they will be to a great extent self-limiting, there would be no risk to health in allowing the use of cyclamates in food without statutory limitation, except for that already laid down in the Soft Drinks Regulations, 1964. We *recommend* accordingly.

4. We do not *recommend* any amendment to the ban on the use of artificial sweeteners in ice-cream.

5. We further *recommend* that any regulations made as a result of this report should be reviewed five years after the date of making.

*November*, 1965

FAC/REP/3

## REPORT OF THE PHARMACOLOGY SUB-COMMITTEE

### Introduction

1. We made an interim report in the following terms:

" We have considered the additional evidence * about the use of cyclamates which has been submitted to the Ministry of Agriculture, Fisheries and Food.

We do not consider that this evidence justifies the reversal of the advice previously given to Ministers that the use of cyclamates in soft drinks up to the maximum limits prescribed by the Regulations does not constitute a hazard to health.

Since, however, the previous advice was not given by the Pharmacology Sub-Committee, we should like to review all the evidence and meanwhile we recommend that the unrestricted use of cyclamates in food should not be permitted."

(* References (7) and (11).)

### Present U.K. Legal Position

2. The Artificial Sweeteners in Food Order, 1953 in effect prohibits the sale of any food containing any artificial sweetener except saccharin. From 2nd June, 1965, manufacturers have been allowed to sell soft drinks sweetened with cyclamates as well as saccharin—either alone or in combination. Full details are given in the Soft Drinks Regulations, 1964(1). For example, for ready-to-drink soft drinks (Regulations, Schedule 2) the maximum permitted quantity of cyclamic acid if used alone is 933 grains (or its equivalent in terms of sodium or calcium cyclamates i.e. about 1,050 grains) per 10 gallons of drink. (1,333 grains for brewed ginger beer and herbal and botanical beverages.) The amount of cyclamic acid permitted is reduced if saccharin is used in combination with it (Regulations, Schedule 2 part III). However, no maximum limit is specified for diabetic and low-calorie soft drinks (Regulations, 5(4) and 5(5)). A soft drink which contains artificial sweetener must either be labelled to indicate that it contains " permitted artificial sweetener " or to reveal the name of the artificial sweetener actually added (Regulations, 13).

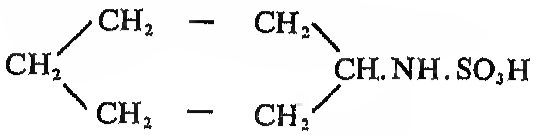
3. Ministers intended to introduce new Artificial Sweeteners regulations to permit cyclamates in food generally, as well as in soft drinks, but delayed any decision pending our full review of available evidence. (Hansard, House of Commons *712* (118) Cols. 1435, 1436 19th May, 1965.)

### Position in the United States

4. In the U.S.A., sodium, calcium and magnesium cyclamates are " generally recognised as safe " and are permitted ingredients in standards for artificially sweetened canned fruits and preserves; but they are not included in standards of identity for some other foods, e.g. fruit juices, cacao and bakery products. Cyclamates and saccharin appear to be allowed generally in foods labelled for special dietary use and both types of artificial sweetener are understood to be on sale directly to the public. The U.S. Food and Drug Administration's Bureau of Medicine and Division of Toxicological Evaluation has recently concluded that " there is no evidence that cyclamates at present use levels are a hazard to health "(2).

### Composition and Purity

5. The structural formula for cyclamic acid is



Similarly, sodium cyclamate is $C_6H_{12}N.SO_3Na$ and calcium cyclamate is $C_{12}H_{24}N_2S_2O_6Ca.2H_2O$. Beck(3) gives the following values for the solubility (g/100 cc) of calcium and sodium cyclamates in various solvents at 25°C.

TABLE 1

| *Solvent* | *Calcium Cyclamate* | *Sodium Cyclamate* |
|---|---|---|
| Water at 25°C ... ... | 24 | 21 |
| 25 per cent ethanol ... ... | 25 | 16 |
| 50 per cent ethanol ... ... | 25 | 14 |
| 75 per cent ethanol ... ... | 15 | 1 |
| Absolute ethanol ... ... | 1·7 | insoluble |
| Propylene glycol ... ... | 70 | 4·3 |

Neither salt has any appreciable solubility in oils or in non-polar solvents. Beck states that the properties of sodium and calcium cyclamates are characteristically those of strong electrolytes and that they are stable to heat in baking and boiling processes, even under acid conditions (above pH 2). Their sweetening power is about thirty times that of sucrose.

6. The Soft Drinks Regulations, 1964 include (at Schedule 1) specifications for the permitted artificial sweeteners, including specifications for cyclohexylsulphamic acid (cyclamic acid), calcium cyclamate and sodium cyclamate. Shortly after the Soft Drinks Regulations were made, monographs on cyclamic acid, sodium cyclamate and calcium cyclamate were published in the Addendum to the British Pharmacopoeia, 1963. It seems likely that these monographs will be adopted for future regulations. (The difference between them and the specifications in the Soft Drinks Regulations is negligible.) The American Food Chemicals Codex sets a limit of 30 p.p.m. selenium for cyclamates (and for saccharin).

**Potential Usage of Cyclamates**

7 (a) Bottle(4) gives some potential uses for cyclamates, e.g. soft drinks, canned foods, pickles and sauces, jams and jellies, pastries, meringues.

(b) It has been calculated that potentially cyclamates might replace about 100,000 tons (3 to 4 per cent) of total U.K. annual sugar consumption. Since cyclamates are about thirty times sweeter than sugar, this represents a potential average daily intake of about *175* mg of cyclamate per person.

(c) In the United States, in terms of sweetening power, total sales of artificial sweeteners are said to be equivalent to about 3½ per cent of sugar consumption.

(d) The U.K. market for saccharin has been quoted by The Financial Times (5.4.65) as 300 tons per annum. Complete replacement by cyclamates would mean an average intake of about *290* mg of cyclamate per person per day.

(e) Total U.K. sugar consumption amounts to about 2 lb per person per week. If half were replaced by cyclamate, this would lead to an average daily intake of *2 g* cyclamate per person.

(f) The average U.K. consumption of soft drinks (as ready-to-drink equivalent) is about 4 fl. oz. per person per day. With a " normal " type of soft drink, sweetened with sugar and cyclamate only, this could lead to an average intake of about *170* mg cyclamate per person per day. A glass (8 fl. oz.) of a " normal " soft drink would contain about *340* mg of cyclamate but a glass of a low-calorie or diabetic soft drink could contain double this amount.

It seems reasonable to suggest that the highest potential intake might occur via the consumption of soft drinks, especially low-calorie or diabetic soft drinks. Intakes would of course be reduced if cyclamates were used in combination with saccharin. For example, if used in a recommended ratio of 10 cyclamate to 1 saccharin (4) all the values for potential intake of cyclamate given above could be approximately halved.

## Toxicological Information

The following paragraphs outline the main points from the available information. Further details and additional information are given in the original articles, all of which were made available to us.

8. *Acute toxicity*

TABLE 2

| Animal | Route of Administration and compound tested | $LD_{50}$(g/kg) or (effect) | Reference |
|---|---|---|---|
| Rat ... | Oral, sodium cyclamate ... | 6 | 5 |
| Rat ... | Oral, sodium cyclamate ... | 12 | 6 |
| Mouse ... | Oral, sodium cyclamate ... | 10–12 | 6 |
| Cat ... | Oral, sodium cyclamate ... | (2 to 3 g/kg produced occasional vomiting only) | 6 |
| Rat ... | Intravenous, sodium cyclamate | Approx. 3·5 | 6 |
| Mouse ... | Intravenous, sodium cyclamate | 4 | 6 |
| Rat ... | Subcutaneous injection, 0·1 g. calcium cyclamate | (extensive necrosis) | 7 |
| Man ... | Intravenous, sodium or calcium cyclamates | (1 g., without ill-effect) | (8) (9) |
| Man ... | Oral, calcium cyclamate ... | (Up to 12 g. No effect except soft stools) | (10) |

9. **Sub-acute toxicity and short-term studies**

TABLE 3

| Animal | Route of Administration | Intake | Duration | Principal Effects Reported | Reference |
|---|---|---|---|---|---|
| Rat ... ... | Stomach tube, daily | 1 g/kg of *sodium* cyclamate | 21 days | No deaths, blood and urine normal. | 6 |
| Rat ... ... | In diet ... | 5% or 10% of *calcium* cyclamate | 6 months so far (still in progress) | Growth depression and effects on reproduction. | 11 & 11A |
| Rat ... ... | In diet ... | 1%, 2% and 3% *sodium* cyclamate | 11 months | No effect on growth rate or kidney and liver weight. No effect on reproduction over three generations. Occasional laxative effect at 2%, more frequent at 3%. | 12 |
| Dog ... ... | In horsemeat ... | 0·5 g/kg body-weight daily | 11 months | No effect on weight, blood, liver and kidney function or urine. | 12 |
| Dog ... ... | In horsemeat ... | 2 g/kg and 4 g/kg of *sodium* cyclamate | (?) | Vomiting, watery stools. | 6 |
| Dog ... ... | Stomach tube... | 2 g/kg and 4 g/kg of *sodium* cyclamate | 21 days | Clinical and histological findings normal. | 6 |
| Dog ... ... | Orally, in meat | 0·5 g or 1 g daily of *sodium* cyclamate | 15 months | Liver and kidney function tests normal. Blood and urine studies no different from controls. Gross and microscopic examination of important organs negative. | 8 |
| Man (two healthy medical students) | In food ... | 5 g of *calcium* cyclamate daily in doses of 3 × 1·5 g and 1 × 0·5 g | 18 days | Clinical and laboratory studies negative. | 8 |
| Man (six healthy medical students) | Orally, as tablets | 5 g of *calcium* cyclamate daily in doses of 1 g, 2 g, and 2 g, at meal-times | 7½ months | No unusual symptoms except that stools increased in bulk and became mushy without increase in number of bowel movements. | 8 |

TABLE 3—*cont.*

| Animal | Route of Administration | Intake | Duration | Principal Effects Reported | Reference |
|---|---|---|---|---|---|
| Man ... ... | Orally ... ... | 5 g to 12 g of *calcium* cyclamate | 14 to 21 days | Soft and mushy stools. Increase in mean stool weight. No significant effect on frequency of bowel movements. | 10 |
| Man (healthy and nephritic) | Intravenous ... | 1 g *calcium* cyclamate | one dose | No detrimental effects nor impairment of renal function. | 9 |
| | then Orally ... | 5 g *calcium* cyclamate daily | 2 weeks | | |
| | and finally Intravenous | 1 g *calcium* cyclamate | one dose | | |
| Children ... | Oral (capsules and soft drinks) | 1 to 1·5 g/30 lb body-weight daily | 24 weeks | No adverse effects on body weight or physical and laboratory findings (including eyesight). Softer stools noted at higher level of intake. | 13 |

## 10. Long-term studies

TABLE 4

| Animal | Route of Administration | Intake | Duration | Principal Effects Reported | Reference |
|---|---|---|---|---|---|
| Rat ... ... | In diet ... | 0·01%, 0·1%, 0·5%, 1% and 5% of *sodium* cyclamate | Life Span | Slight retardation of growth and marked diarrhoea at the 5% dietary level. | 14 |
| Rat ... ... | In diet ... | 0·01%, 0·1%, 0·5%, 1% and 5% of *sodium* cyclamate | 2 years | Mortality equal to controls. No effect on organ weights at the 5% level, slight growth retardation, marked diarrboea and, histopathologically, slight inanition. | 15 |
| Rat ... ... | In diet ... | 0·05%, 0·1% and 1% of *sodium* cyclamate | 1½ to 2¼ years | Weight gains normal or near-normal; clinical and histopathological studies showed no differences from controls; Normal litters raised—experiment conducted into the third generation at the 0·05% dietary level. | 6 |

NOTE: FAO/WHO toxicological evaluations assume, for the rat, that 1 per cent in the diet is equivalent to 500 mg./kg. body-weight.

## 11. Metabolic and other pharmacological studies

TABLE 5

| Test | Principal Effects Reported | Reference |
|---|---|---|
| *Isolated rabbit intestine and isolated frog heart* | No effects of *sodium* cyclamate except those due to the physical action of a hypertonic solution which could be duplicated by using an equivalent concentration of an inert salt, e.g. sodium chloride. | 6 |
| *Blood pressure and respiration* (dog and cat) | Intravenous injections of 100–200 mg/kg of *sodium* cyclamate to anaesthetized dog and 250 mg/kg to anaesthetized cat did not change blood pressure or pulse rate. | 6 |
| *Central nervous system* (rabbit) | 0·5 cc of 1·25 per cent solution of *sodium* cyclamate given intracisternally to a rabbit had no effect. 0·5 cc. of a 2·5 per cent solution resulted in transitory convulsion followed by recovery. | 6 |
| *Digestive enzymes* ... | 1 per cent *sodium* cyclamate has no appreciable effect *in vitro* on the digestive action of pepsin or trypsin and slightly enhances the digestive action of diastase and lipase. | 6 |

TABLE 5—*cont.*

| Test | | Principal Effects Reported | Reference |
|---|---|---|---|
| *Excretion* (rabbit) | (i) | *Sodium* cyclamate excreted unchanged to the extent of 80 per cent–90 per cent in 12 hours in the urine of rabbits when given intravenously, intraperitoneally or orally. | 16 |
| (rat) | (ii) | *Sodium* cyclamate excreted unchanged in urine of rats. | 17 |
| (rat) | (iii) | Single doses of *sodium* cyclamate up to 3·2 g/kg intraperitoneally rapidly excreted by the *rat* in 24 hours. A dose of 1·4 g/kg excreted with equal rapidity by normal and unilaterally nephrectomized *rats*. | 17 |
| (rat) | (iv) | *Rats* were given repeated oral doses of 80 to 120 mg/kg *sodium* cyclamate for 5 consecutive days. An average of 85 per cent was excreted in 5 days and another 3 per cent in the 4 days following the last dose. About two-thirds was excreted in the faeces and the remainder in the urine. | 17 |
| (rat) | (v) | Single oral doses of 0·5 to 2 g/kg body weight of *sodium* and *calcium* cyclamates excreted to extent of 30 per cent in urine and 70 per cent in faeces in 3 days (substantially in first 24 hours). Laxative dose (ED50) about 1·9 g/kg for sodium cyclamate and 2·8 g/kg for calcium cyclamate. | 12 |
| (dog) | (vi) | Single doses by stomach tube of 0·75 to 1 g/kg *sodium* cyclamate; 16 per cent–65 per cent excreted in urine in 11–17 hours. Laxative effect between 0·75 to 1 g/kg body weight. | 12 |
| (healthy man) | (vii) | In seven days 79·5 per cent of an oral dose to a *human* of 300 mg of *sodium* cyclamate was found in the urine, 26 per cent being excreted in the first 24 hours. A total of 77 per cent was recovered in 3 days after an oral dose of 200 mg. | 6 |
| (healthy man) | (viii) | After intravenous administration of 1 g. of sodium cyclamate 70 per cent–90 per cent was excreted in the urine within 3 hours. | 8 |
| (healthy man) | (ix) | Following a single oral dose of *calcium* cyclamate, 31·2 per cent was excreted in the urine and 65·45 per cent in the faeces after 3–4 days. | 8 |
| (healthy man) | (x) | In subjects consuming 5 g of *calcium* cyclamate daily, as part of a 7½ month toxicity study, analysis of 24 hour urine samples at monthly intervals indicated an average excretion in the urine of 37 per cent of the daily dose. | 8 |
| (normal and nephritic patients) | (xi) | Subjects received 1 g of *calcium* cyclamate intravenously, followed by 5 g orally for two weeks, then 1 g intravenously. In the two normal subjects mean excretion was 79·4 per cent prior to 2 weeks of oral ingestion and 81 per cent after 2 weeks. For seven patients the mean excretion was 86·7 per cent prior to 2 weeks of oral ingestion and 93·3 per cent after. Daily urinary excretion for 3 patients was approximately 13 per cent of the ingested oral dose of 5 g calcium cyclamate compared with 31 per cent in the two normal subjects. | 9 |

12. *Tissue Retention and Cumulation*

(a) Intravenous injection of *sodium* cyclamate tagged with radioactive sulphur showed that with the exception of the kidney and perhaps the liver, there was no significant concentration in the various organs of the rat, rabbit and dog. Sodium cyclamate penetrated into the brain with difficulty but was found in the foetus of the rat(17). J. D. Taylor(18) has calculated the amounts of cyclamate remaining in the body after 2 or 5 or 10 g doses each day at daily excretion rates ranging from 10 per cent to 90 per cent. For example, with a 5 g daily intake and 75 per cent excretion rate, it is calculated that 1·67 g cyclamate will remain in the body at 1 week and also at infinite time.

(b) Norton[19] has estimated the potential effects of the cyclamate radicle and sodium and calcium ions on patients with renal failure—assuming that the rate of elimination of cyclamates for such patients is about one-fifth normal. Norton estimated that an intake of 7½ g of cyclamate was unlikely to do any harm. Richards, Hwang and Taylor [20] suggest that toxic effect on the kidneys of humans is unlikely.

(c) As shown in Table 5, Dedmon, Ryan and Kark[9] have made a special study of the excretion of calcium cyclamate in nephritic patients.

13. Schoenberger, Rix, Sakamota, Taylor and Kark[8] studied the effect on calcium and phosphorus balance on human subjects given 5 g calcium cyclamate daily.

*Conclusions*

14. We were impressed by the extent of the information that is available to support the safety-in-use of cyclamates. We noted the specifications available in the current Soft Drinks Regulations and in the Addendum to the British Pharmacopoeia and agreed to suggest that cyclamates for use in food should not contain more selenium than is practicable. In general, adequate information is available from results of acute, short-term, and metabolic studies on man and on various species of animals; but, as regards long-term studies, only information from the feeding of rats is available.

15. From the information available we consider that ingestion of cyclamates is unlikely to present a hazard to health though they may exert a laxative effect if consumed in substantial amounts. Further work on the mechanism of this laxative effect is desirable. It seems unlikely that the effect would occur unless daily intakes were above 50 mg cyclamate/kg body-weight. We would therefore accept the use of cyclamates in food (including soft drinks and other beverages) at daily intakes below this level provided that long-term feeding studies on a second species (e.g. the mouse) and injection tests on rats are carried out and that results become available within 5 years. We have not studied exhaustively the possible nutritional aspects of any prolonged unrestricted use of cyclamates but consider that there should not be cause for concern within the limit we have recommended.

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